The amendments to claims 2 and 15 are supported by the application as filed. Placental bikunin is described throughout the specification, including at, for example, page 3 under "Summary of the Invention": "This invention describes a method for the production of glycosylated placental bikunin." Additionally, the first sentence of the last paragraph on page 3 states: "This invention is illustrated with a truncated placental bikunin having the amino acid sequence shown in Figure 2." Moreover, page 4, line 2 states: "The monokunin may be derived from or may be a fragment of a known bikunin," including the placental bikunin described in the specification. Accordingly, the amendments to claims 2 and 15 do not add new matter to the application.

2. Objection to the Specification

The Patent Office objected to the specification because "patent application numbers remain in the disclosure." Please note that no patents have yet issued from the remaining patent applications referred to by patent application number. If and when patents issue therefrom, the patent application numbers will be replaced by patent numbers.

3. Claim Rejections – 35 U.S.C. § 102

The Patent Office rejected claims 2 and 6-9 under 35 U.S.C. § 102(b) as anticipated by Kawaguchi et al. "because the primary amino acid sequence of human hepatocyte growth factor activator inhibitor type 2 [as disclosed in Kawaguchi] is identical to instant SEQ ID NO:1 and because the protein is purified from human cells, it inherently is glycosylated." The Office further offered two references as evidence of inherency: "The glycosylation pattern and sialic acid content is an inherent feature of mammalian bikunin; indeed, the literature recognizes that

bikunin contains sialic acid (see, e.g., Yuki et al.) and that it contains N-acetylneuraminic acid (see, e.g., Hochstrasser et al., page 1360, first paragraph)."

According to the Federal Circuit, "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities.'" *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citation omitted). Furthermore, according to the Board of Patent Appeals and Interferences, "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

In this case, the independent claim (claim 2) has been amended to recite a placental bikunin protein that contains at least one sialic acid residue. The protein corresponding to SEQ ID NO:1 is an example of a placental bikunin protein. In contrast, both references cited by the Office as evidence of inherency, Yuki et al. and Hochstrasser et al., disclose only urinary bikunin (also referred to as inter-α-trypsin inhibitor), which is an entirely different protein. For example, the amino acid sequences of the proteins share little, if any, homology. This can be seen through a comparison of the amino acid sequences for placental bikunin (see SEQ ID NO:1 in the present application) and urinary bikunin (see Fig. 1 in Hochstrasser; see GenBank Accession No. 2124279A for complete sequence). Since the references offered by the Office as extrinsic evidence of inherency do not teach sialic acid residues in placental bikunin, the Office has not met its burden of showing that "the allegedly inherent characteristic necessarily flows from the

teachings of the applied prior art," as required under *Robertson* and *Levy*. Accordingly, the applicants respectfully request withdrawal of the novelty rejection.

4. Claim Rejections – 35 U.S.C. § 103

The Patent Office rejected claims 15, 18-21, and 26 under 35 U.S.C. § 103(a) as unpatentable over Gentz et al. in view of Gribben et al. and Hotchkiss et al. In particular, the Office stated: "First, as discussed above, human bikunin is known to be a glycoprotein that has sialic acid residues when produced in mammalian cells," referring to its discussion of Yuki et al. and Hochstrasser et al. in the context of its novelty rejection.

According to the Federal Circuit, "The PTO bears the burden of establishing a case of *prima facie* obviousness. A *prima facie* case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art." *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993). Moreover, "To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03 (citing *In re Royka*, 490 F.2d 981 (C.C.P.A. 1974)).

In this case, the independent claim (claim 15) has been amended to recite a placental monokunin protein that contains at least one sialic acid residue. And, as noted above, Yuki and Hochstrasser describe only urinary bikunin. Therefore, the cited references do not show that placental bikunin or monokunin inherently contains sialic acid residues. Furthermore, neither do Gentz, Gribben, or Hotchkiss. Since none of the cited prior art references teaches sialic acid modification of placental bikunin or monokunin, the combination of Gentz with Gribben, Hotchkiss, Yuki, and/or Haschstrasser does not teach or suggest all the claim limitations.

Therefore, the Patent Office cannot establish a *prima facie* case of obviousness based upon these references. Accordingly, the applicants respectfully request withdrawal of the obviousness rejection.

5. Conclusion

In view of the amendments and remarks above, the application is considered to be in good and proper form for allowance. Therefore, the Patent Office is respectfully requested to pass the application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of this application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

Dated: January 22, 2002

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Appendix A: Marked-Up Version of Replacement Paragraph

1. Page 2, first paragraph:

Placental bikunin, a novel human serine protease inhibitor containing two Kunitz-like domains, has been cloned and expressed (Delaria et al., J. Biol. Chem. 272(18): 12209-12214, 1997). Characterization studies showed that truncated placental bikunin is a potent inhibitor of kallikrein and plasmin. The sequence of truncated placental bikunin is shown in Figure 2. The protease inhibitory function of bikunin suggests that placental bikunin has important therapeutic application for the treatment of a variety of disorders including prevention of disseminated intravascular coagulation, reduction of blood loss during surgery, reduction of brain edema following vascular injury, and blockage of tumor growth and invasiveness (Marlor et al., J. Biol. Chem. 272(18): 12202-12208, 1997). An unexpected observation was made recently that placental bikunin was able to increase airway surface liquid osmolarity and mucociliary transport in animal models [~~(United States patent application serial number 09/144,428 to Tamburini et al., filed August 31, 1998, entitled "Human Bikunin.")~~] (U.S. Patent Application No. 09/441,966, filed November 17, 1999, entitled "Method for Accelerating the Rate of Mucociliary Clearance"). Thus there is a need to produce placental bikunin in large quantities.

Appendix B: Clean Version of the Pending Claims

2. (Twice Amended) An isolated mammalian glycosylated bikunin, wherein the glycosylated bikunin is a placental bikunin and comprises at least one sialic acid residue.

6. The glycosylated bikunin of claim 2 wherein the glycosylated bikunin comprises at least one sialic acid residue bonded within the glycosylated bikunin via an alpha-(2,3) linkage.

7. The glycosylated bikunin of claim 2 wherein the glycosylated bikunin comprises at least one sialic acid residue bonded within the glycosylated bikunin via an alpha-(2,6) linkage.

8. The glycosylated bikunin of claim 2 wherein the glycosylated bikunin comprises at least one sialic acid residue bonded within the glycosylated bikunin via an alpha-(2,3) linkage and at least one sialic acid residue bonded within the glycosylated bikunin via an alpha-(2,6) linkage.

9. The glycosylated bikunin of claim 2 in a pharmaceutically acceptable carrier.

15. (Twice Amended) An isolated mammalian glycosylated monokunin, wherein the glycosylated monokunin is a placental monokunin and comprises at least one sialic acid residue.

18. The glycosylated monokunin of claim 15 wherein the glycosylated monokunin comprises at least one sialic acid residue bonded within the glycosylated monokunin via an alpha-(2,3) linkage.

19. The glycosylated monokunin of claim 15 wherein the glycosylated monokunin comprises at least one sialic acid residue bonded within the glycosylated monokunin via an alpha-(2,6) linkage.

20. The glycosylated monokunin of claim 15 wherein the glycosylated monokunin comprises at least one sialic acid residue bonded within the glycosylated monokunin via an alpha-(2,3) linkage and at least one sialic acid residue bonded within the glycosylated monokunin via an alpha-(2,6) linkage.

21. The glycosylated monokunin of claim 15 in a pharmaceutically acceptable carrier.

25. The glycosylated bikunin of claim 2, wherein the glycosylated bikunin comprises at least one N-acetylneuraminic acid residue.

26. The glycosylated monokunin of claim 15, wherein the glycosylated monokunin comprises at least one N-acetylneuraminic acid residue.

Appendix C: Rewritten Claims With Markings to Show Changes Made

2. (Twice Amended) An isolated mammalian glycosylated bikunin, wherein the glycosylated bikunin is a placental bikunin and comprises at least one sialic acid residue.

15. (Twice Amended) An isolated mammalian glycosylated monokunin, wherein the glycosylated monokunin is a placental monokunin and comprises at least one sialic acid residue.